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Risk of diffuse large B-cell lymphoma after solid organ transplantation in the United States

Todd M. Gibson, Ph.D.[1,2,*], **Eric A. Engels, M.D., M.P.H.**[1], **Christina A. Clarke, Ph.D., M.P.H.**[3,4], **Charles F. Lynch, M.D., M.S., Ph.D.**[5], **Dennis D. Weisenburger, M.D.**[6], and **Lindsay M. Morton, Ph.D.**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland [2]Cancer Prevention Fellowship Program, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland [3]Cancer Prevention Institute of California, Fremont, California [4]Department of Health Research and Policy and Medicine, Stanford University School of Medicine, Stanford, California [5]Department of Epidemiology, University of Iowa, Iowa City, Iowa [6]Department of Pathology, City of Hope National Medical Center, Duarte, California

Abstract

Non-Hodgkin lymphoma (NHL) arising in the context of immunosuppression is an important adverse outcome following solid organ transplantation. Diffuse large B-cell lymphoma (DLBCL) is the most commonly diagnosed subtype of post-transplant NHL, but few studies of transplant recipients have examined subtype-specific risks. Therefore, we examined DLBCL risk in the Transplant Cancer Match Study, including registry-based cancer ascertainment among 96,615 solid organ transplants performed from 2000–2008. We determined standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) comparing DLBCL risk in transplant recipients to that in the general population, and used multivariable Poisson regression models to assess the impact of potential risk factors. We identified 321 incident cases of DLBCL, over 12 times more than expected based on general population rates (SIR=12.6, 95% CI=11.2–14.0). SIRs were highest in young recipients and those receiving a lung or pancreas/kidney-pancreas transplant, and were greatly elevated for extranodal DLBCLs at the site of the transplant compared to other sites. DLBCL risk was highest in the first year following transplant, and SIRs for early-onset DLBCL risk were elevated in association with EBV negative serostatus and use of polyclonal antibody induction therapy. In conclusion, associations between recipient and transplant factors and post-transplant DLBCL risk suggest a complicated interrelationship among multiple risk factors and timing of disease.

Corresponding author: Todd M. Gibson, Ph.D., 262 Danny Thomas Place, Mail Stop 735, Memphis, TN 38105 USA, Todd.Gibson@stjude.org, Phone: +1 (901) 595-8260, Fax: +1 (901) 595-5845.

*Current affiliation: Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee

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Keywords

organ transplant; non-Hodgkin lymphoma; diffuse large B-cell lymphoma; immunosuppression; Epstein-Barr virus

Introduction

Over 28,000 solid organ transplants are performed annually in the United States (1). Improved survival of transplant recipients in recent decades is due in large part to the effectiveness of current immunosuppressive therapies in preventing organ rejection, but the acute and long-term immunosuppression also increases recipients' risk of a number of malignancies (2–7). In particular, post-transplant lymphoproliferative disorder (PTLD) is a major cause of morbidity and mortality in transplant recipients (8). Epstein-Barr virus (EBV) is prominent in the etiology of PTLD (9), but recipient age, variations in pharmacologic immunosuppression, and type of organ transplanted have also been associated with PTLD risk (8, 10). In addition, some studies have suggested important differences in disease characteristics by time of onset (11–17), EBV involvement (12, 13, 15, 18, 19) or primary site of disease (20–23).

Most previous research on lymphoma risk in transplant recipients has focused on PTLD or non-Hodgkin lymphoma (NHL). However, PTLD comprises a group of clinically and molecularly heterogeneous diseases ranging from plasmacytic hyperplasia to malignant NHL (24), and NHL includes numerous subtypes that have been shown to have different etiologies in the general population (25), as well as varying risks after transplantation (26–28). Immunosuppression has been associated with strikingly high risks of diffuse large B-cell lymphoma (DLBCL), a common and clinically aggressive lymphoma (29). A previous population-based study found a significantly increased risk of DLBCL after kidney transplantation, but did not include other organ transplants or examination of risk factors (30).

We therefore examined risk for DLBCL among solid organ transplant recipients. We used data from the Transplant Cancer Match Study, which includes systematic registry-based ascertainment of cancer in transplant recipients and data on a range of possible risk factors (3). We restricted our analysis to transplants performed during 2000–2008 because clinical practice regarding transplantation and immunosuppression has changed considerably over time, and because of increased availability of data on EBV status in more recent years. We included examination of risks by recipient EBV serostatus, timing of DLBCL onset, and primary site of disease.

Materials and Methods

Transplant Cancer Match Study

The Transplant Cancer Match Study (www.transplantmatch.cancer.gov) has been described previously (3). Briefly, linkage was performed between the Scientific Registry of Transplant Recipients (SRTR), which collects data on all solid organ transplants in the United States, and 14 population-based U.S. cancer registries. Computer-based linkage was based on

subjects' name, sex, date of birth, and social security number, and was followed by manual review of potential matches. Transplant recipients residing in the geographic coverage area of the cancer registries were included, and cancer ascertainment was at least 95% complete throughout follow-up (3).

For this analysis, we quantified risk of DLBCL in a cohort of 96,615 solid organ transplants performed from 2000–2008, representing over 40% of all solid organ transplants in the United States during that time. Recipients included in the Transplant Cancer Match Study were similar to those outside the linked cancer registries (3). The study was approved by human subjects committees at the National Cancer Institute and, as required, participating cancer registries (3).

Cancer Ascertainment and Risk Factor Data

Incident cases of DLBCL among transplant recipients were identified from the 14 linked population-based cancer registries using International Classification of Diseases for Oncology, Third Edition (ICD-O-3) morphology codes 9678–9680 or 9684 (31). Primary DLBCL site was classified as nodal or extranodal using ICD-O-3 topography codes, and extranodal cases were further classified as arising at the transplanted organ ("transplant-site DLBCL") or at any other extranodal site ("extranodal DLBCL"). Recipients with missing codes or determined to have multiple organs involved but with unknown primary site of origination (codes C779 and C809) were categorized as having extranodal disease. The assignment of transplant-site DLBCL was based solely on organ concordance (e.g., DLBCL of any kidney in a kidney recipient), as it was not always possible to determine whether the DLBCL arose in the donor or remaining native organs.

Data on risk factors were obtained from the SRTR records, including recipient characteristics (sex, age at transplant, race/ethnicity) and transplant characteristics (organ, number, calendar year). EBV serostatus of transplant recipients was available for 58% of transplants performed after 1999. Immunosuppressive medication use at initial discharge was obtained from SRTR as well, and induction therapies were categorized as either polyclonal antibodies or IL-2 receptor antagonists (monoclonal antibodies and alemtuzumab were used too infrequently to include in the analyses). Drugs typically used in the maintenance phase of immunosuppression, such as cyclosporine, tacrolimus, and mycophenolate mofetil, were not included in these analyses due to the high likelihood of changes in these medications after transplant (32).

Statistical Analyses

Follow-up for cancer risk started at the date of transplantation and continued until the earliest of death, failure of a transplanted organ, a subsequent transplant, loss to follow-up, or the last date of cancer registry coverage. Recipients were considered at risk separately during successive transplant episodes, and were not censored upon first cancer diagnosis unless the first cancer was NHL.

We compared risk of developing DLBCL among transplant recipients to that of the general population by calculating standardized incidence ratios (SIR = number of cases observed in the transplant cohort/number of cases expected in the general population). Expected counts

were obtained by applying general population DLBCL rates to the person-time at risk among transplant recipients, stratified by sex, age (5-year intervals), race/ethnicity, calendar year, and cancer registry (3). Ninety-five percent confidence intervals (95% CI) were obtained using an exact method assuming a Poisson distribution for the observed count (33). Incidence rates (IRs) were also calculated as observed cases/person-years of follow-up.

We examined the impact of possible risk factors for DLBCL by calculating IRs, SIRs and 95% CIs among strata of these factors. Primary analyses estimated relative risks (RRs) by comparing SIRs among different strata in multivariable Poisson regression models, adjusted for sex, race/ethnicity, age at transplant, type of organ transplanted, and calendar year. Given the expected importance of recipient EBV serostatus and the potential for residual confounding due to missing data, we included comparisons after stratification by recipient EBV serostatus. We also stratified by time period after transplant. “Early-onset DLBCL” was defined as disease diagnosed within two years of the transplant date, whereas DLBCL diagnosed after two years was termed “late-onset”. For analyses stratified by primary anatomic site of DLBCL, site-specific SIRs were calculated for transplant-site DLBCL, extranodal DLBCL, and nodal DLBCL, with distinct expected values calculated for each category. Site-specific analyses of DLBCL were restricted to the major transplanted organ types (kidney, pancreas-kidney, liver, heart, and lung).

To assess whether the effects of risk factors differed by time of disease onset or primary DLBCL site, we tested for interactions with the relative risks by fitting separate Poisson regression models to the different cohorts (e.g., early-onset disease and late-onset disease), then combining the cohorts and using the corresponding scores to compute a robust variance estimate for all model parameters that accounted for the repeated use of the same individuals (34). Differences between association parameters for early- versus late-onset DLBCL or transplant site versus other site DLBCL were then assessed using a Wald test. All analyses were conducted using SAS statistical software version 9.1.3 (SAS Institute, Inc.), and significance of associations was based on $\alpha < 0.05$.

Results

We examined a cohort of 96,615 transplants performed in the U.S. from 2000–2008 (median follow-up time = 2.5 years). As shown in Table 1, 61% of transplant recipients were male, 8% were age 0–19 years at time of transplant (median age at transplant = 49 years), and the most commonly transplanted organs were kidney (59%), liver (22%), and heart (8%).

We identified 321 incident cases of DLBCL, over 12 times more than expected based on rates in the general population (SIR=12.6, 95% CI=11.2–14.0; Table 1). DLBCL was the most common NHL subtype in transplant recipients, comprising 63% of all NHL cases. IRs for DLBCL were high in the youngest transplant recipients, decreased with increasing age at transplant until age 40–49, and then rose steadily with increasing age. In contrast, risk relative to the age-matched general population was greatly increased in the youngest recipients (SIR=1738 for age 0–9 years), and decreased continuously with increasing age at transplant, to an SIR of 5.3 in the oldest recipients (age 70+ years). SIRs were modestly

higher for females compared to males (P=0.05), and for non-Hispanic whites compared to other racial/ethnic groups (P=0.01).

DLBCL risk was strongly associated with type of organ transplant (Poisson regression P<0.001) and recipient EBV serostatus (P<0.001), including adjustment for age at transplant and other factors (Supplemental Table 1 shows the distribution of organ type by age at transplant). The highest elevations in risk were for lung transplants (SIR=41.3), pancreas/kidney-pancreas transplants (SIR=33.1), and EBV seronegative recipients (SIR=43.6; Table 1). Overall, DLBCL risk did not differ significantly by transplant number, year of transplant, or use of either polyclonal antibodies or IL-2 receptor antagonists as induction immunosuppressive therapy.

Risk of developing DLBCL was highest during the first year after transplantation (SIR=24.1; Figure 1A). Risks were markedly lower after the first two years and remained relatively constant from three to nine years after transplant. Although EBV seronegative recipients had greater elevations in risk than seropositive recipients during the first year after transplant, both groups experienced the highest risks in this first year (Figure 1B). SIRs decreased dramatically after the first year in both groups, but they continued to decline over nine years of follow-up for EBV seronegative recipients, whereas EBV seropositive recipients showed an increasing trend after three years post-transplantation. Similar patterns were observed regardless of the type of organ transplanted (not shown).

When considering recipient EBV serostatus and time period after transplant (Table 2), the risk for early-onset DLBCL was significantly higher (P<0.001) in EBV seronegative recipients (SIR=78.7) than in EBV seropositive recipients (SIR=11.8). In contrast, the risk for late-onset DLBCL was not significantly different between EBV seronegative (SIR=11.4, not shown) and seropositive (SIR=6.7) recipients. Few cases of late-onset disease were identified in EBV seronegative recipients (N=11), preventing further examination of risk factors within this group.

For early-onset DLBCL, the pattern of strikingly high SIRs in the young and declining SIRs with increasing age was evident in both EBV seronegative and seropositive recipients (both P_{trend}<0.001; Table 2). SIRs based on a small number of cases suggested a similar age-dependent risk pattern for late-onset DLBCL, but only EBV seropositive recipients were examined. The highest risks were found following lung transplantation regardless of EBV serostatus and time since transplant, with SIRs for lung recipients approximately four-fold higher than those for kidney recipients. In contrast, the SIRs for DLBCL after liver transplantation were significantly higher than those after kidney transplantation only in EBV-seropositive recipients (regardless of time since transplant). In analyses of specific immunosuppressive medications, use of polyclonal antibody induction therapy was associated with increased risk of early-onset DLBCL in EBV seronegative recipients (RR=2.9, 95% CI=1.6–5.0). In contrast, use of IL2 receptor antagonists was associated with decreased risk of early-onset DLBCL in EBV seropositive recipients (RR=0.5, 95% CI=0.3–0.9). Use of specific immunosuppressive medications was not significantly related to risk of late-onset DLBCL.

Although the incidence of DLBCL occurring in the transplanted organ was low, the SIR was substantially higher for DLBCL occurring in the transplanted organ (SIR=186) compared with other extranodal sites (SIR=13.3) or lymph nodes (SIR=9.7) (Table 3). Patterns of risk by EBV serostatus or transplanted organ did not differ by DLBCL site, although no DLBCLs were identified in the heart following heart transplantation. DLBCLs in the transplanted organ occurred almost exclusively as early-onset disease (97% of 32 cases), with only one case identified more than two years after transplant.

Discussion

We present the first large-scale, population-based study of risk factors for DLBCL following solid organ transplantation. As the most common NHL subtype occurring among transplant recipients and one of the most aggressive forms of PTLD, DLBCL is likely a primary driver of many associations observed in previous studies of transplant-related NHL or PTLD. In addition to negative EBV serostatus of the recipient being a prominent risk factor for DLBCL, we identified that both young age at transplant and transplant of a lung or pancreas were associated with increased risks, regardless of EBV serostatus. Recipients were at greatest risk during the first year after transplant, and both recipient EBV serostatus and use of polyclonal antibodies as induction therapy were associated with risk only in the early-onset period. Risk relative to the general population was also considerably greater for DLBCL occurring in the transplanted organ than for disease at other sites. Furthermore, our results suggest that the impact of induction immunosuppression medications may differ according to EBV serostatus of the recipient.

We found greatly elevated risk of DLBCL in the first year after transplant, similar to previous reports for NHL overall (16, 23). The initial increase in risk we observed soon after transplantation was more dramatic than some previous studies of NHL, likely reflecting both the subtype-specificity of the outcome in our study and the inclusion of organ transplants other than kidneys. The risk of early-onset DLBCL was particularly striking among EBV seronegative recipients, supporting the prominent role of uncontrolled primary EBV infection in lymphomas occurring immediately following transplant (15, 16, 18, 20). A recent study of kidney transplants in Australia reported evidence for two distinct mechanisms of lymphomagenesis, with early disease caused largely by primary EBV infection during acute immunosuppression, and late disease attributed to aberrant proliferation secondary to prolonged immunosuppression (15). Our results generally support this model of lymphomagenesis for development of DLBCL. Although we observed that risk of DLBCL was also greatest in the first post-transplant year for EBV seropositive recipients, the finding may be explained by reactivation of latent EBV infection.

In analyses stratified by EBV serostatus and time since transplantation, we found that risks were highest for early-onset DLBCL among pediatric recipients. Increased risk for those transplanted at a young age has been established for NHL and PTLD, but the increase is typically attributed to the high prevalence of EBV seronegativity in this group. However, we found that young age at transplant was associated with increased DLBCL risk among EBV seropositive recipients, suggesting the young immune system may also be particularly susceptible to immunosuppression-induced EBV reactivation.

Patterns of DLBCL risk by organ type were similar across strata of EBV serostatus and timing of disease onset, with the notable exception of liver transplants. Among EBV seronegative recipients, DLBCL risk was lower for liver transplants than for heart or kidney transplants, whereas liver transplants had higher relative risk of DLBCL among EBV seropositive recipients. Furthermore, among EBV seropositive recipients, only liver transplants had similarly increased risks for both early- and late-onset disease. Our results suggest EBV seronegativity is a risk factor for DLBCL after liver transplantation, but they also support previous findings from studies of NHL suggesting that the role of EBV may differ for liver transplants compared to other types of organ transplant (18, 19). The greater mass of donor lymphatic tissue delivered with a liver transplant has been hypothesized as a possible mechanism explaining the differences in risk by organ (18). We found the highest DLBCL risk among persons receiving lung transplants, which may support the importance of donor lymphoid mass in addition to intensity of immunosuppression. However, in contrast to liver transplants, relative risk in lung transplants remained high regardless of EBV serostatus or timing of DLBCL onset. Detailed examinations of lymphoma risk in lung transplants have not been reported in previous studies.

Induction therapies for the prevention of acute rejection include polyclonal antibodies, which result in severe and prolonged depletion of T-cells, and IL-2 receptor antagonists, which inhibit T-cell activation (35). Use of polyclonal antibodies for induction therapy was associated with increased risk of early-onset DLBCL only among EBV seronegative recipients, suggesting T-cell depletion strongly impairs the immune response to primary EBV infection. A previous study found increased risk of early-onset, but not late-onset, NHL with use of polyclonal antibodies for induction therapy, but did not isolate the association to EBV seronegative recipients (15). The lack of association in EBV seropositive recipients may indicate that polyclonal antibody-induced lymphocyte depletion has a less profound impact on EBV reactivation, but other patient factors influencing choice of immunosuppressive agent may also be important. Our finding that use of IL2 receptor antagonists was associated with reduced risk of early-onset DLBCL in EBV seropositive recipients may be due to chance, as it is not readily explained and has not been reported in previous studies of NHL. Late-onset DLBCL risk is more likely to be influenced by maintenance medications and changes in medication use over time, which were not included in this analysis.

Although DLBCLs occurring at the site of the transplanted organ were uncommon, risk relative to the general population was much higher than for other extranodal sites or lymph nodes. This strong increase is consistent with previous literature (21–23, 36), and supports the idea that chronic antigenic stimulation by the allograft contributes to lymphomagenesis (37), particularly for lung and liver transplants. Notably, almost all DLBCLs in the transplanted organ arose in the first two years post-transplant. DLBCL derived from donor lymphocytes conveyed with the graft could also play a role, although most cases of PTLD are of recipient origin (38). A greater percentage of lymphomas occur extranodally in transplant recipients compared to the general population, and prognosis is poor for extranodal versus nodal disease (23), but we did not find large differences between risk of extranodal DLBCL outside the transplanted organ and risk of nodal DLBCL.

Strengths of this study include the specific focus on DLBCL and the use of population-based registries for ascertainment of both transplants and cancers. The large size of the study enabled restriction of analyses to the most recent and clinically relevant time period, as well as unique examination of risk factors stratified by both EBV serostatus and timing of disease onset. Limitations were primarily based on our use of the transplant and cancer registries for exposure and outcome data, which likely resulted in some misclassification.

The proportion of NHL classified as “not otherwise specified (NOS)” was greater in Transplant Cancer Match Study cases (20.5%) compared to that expected based on population rates (12.4%) (26), and many NHLs classified as NOS are likely DLBCLs. Therefore, the DLBCL-specific IRs and SIRs reported may be underestimates. Induction medications are administered at the time of transplantation and therefore should be captured. However, it is possible that some use of these medications was missed in the reports submitted to the SRTR. We investigated the impact of use of polyclonal antibodies and IL2 receptor antagonists, but had insufficient case numbers to study other types of induction medication. Monoclonal antibodies (e.g., OKT3) have been implicated in post-transplant lymphoma risk (23, 36, 39), but our study was limited to a recent time period in which use of these agents was rare. Our stratified analyses indicated that late-onset DLBCL among EBV seropositive recipients was uncommon, preventing detailed examination of risk factors. Furthermore, residual confounding due to missing EBV serostatus is possible, although we do not expect meaningful differences between recipients with and without EBV serostatus data (Supplemental Tables 2 and 3). We did not have data on EBV viral load during follow-up or tumor EBV status that could allow better characterization of the role of EBV in DLBCL risk.

DLBCL makes up a large proportion of post-transplant NHL and is a primary component of associations observed in previous studies of NHL and PTLD. However, full understanding of post-transplant lymphoma etiology requires characterization of subtype-specific risks (26–28, 30). Our results confirm the prominent role of primary EBV infection in DLBCL risk, particularly in the first two years after transplant, and also show age at transplant and type of organ transplant to be important risk factors regardless of EBV serostatus. Our subtype-specific results provide additional insight into the complicated interrelationship among potential risk factors and lymphoid malignancies following transplantation. Future work is needed to characterize the role of EBV reactivation, and to further investigate the impact of immunosuppressive medication regimens on risk of DLBCL and other NHL subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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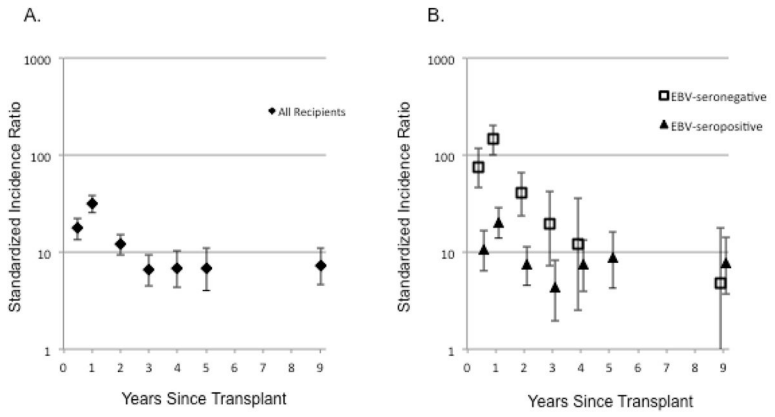

Figure 1.

Figure 1A. Risk of diffuse large B-cell lymphoma by time since transplant in solid organ transplant recipients in the United States. Standardized incidence ratios (SIRs) and associated 95% confidence intervals are shown according to time since transplantation. Each point represents the SIR for the previous time interval, with the point centered on the end of that time interval (6 months, 1, 2, 3, 4, 5, and 9 years post-transplant). The vertical axis shows the standardized incidence ratios on a log-scale.

Figure 1B. Risk of diffuse large B-cell lymphoma by time since transplant in solid organ transplant recipients in the United States, stratified by recipient EBV serostatus. Standardized incidence ratios (SIRs) and associated 95% confidence intervals (CIs) are shown according to time since transplantation and recipient EBV serostatus (open square: EBV seronegative; closed triangle: EBV seropositive). Each point represents the SIR for the previous time interval, with the point indicating the end of that time interval (6 months, 1, 2, 3, 4, 5, and 9 years post-transplant). Time intervals are identical for EBV seronegative and seropositive recipients; the points are offset to allow distinction of 95% CIs. There were no cases among EBV seronegative recipients during the interval between four and five years post-transplant, so this interval was combined with the subsequent 6–9 year interval. The vertical axis shows the standardized incidence ratios on a log-scale.

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Table 1

Associations between recipient and transplant characteristics and risk of diffuse large B-cell lymphoma in solid organ transplant recipients from 2000–2008 in the United States

	Transplant Recipients n (%)[a]	DLBCL Cases n (%)[a]	IR[b]	SIR	95% CI
All transplants	96615	321	115	12.6	11.2–14.0
Age at transplant					
0–9	3524 (4)	21 (7)	192	1738	1076–2657
10–19	4335 (4)	29 (9)	229	360	241–517
20–29	6840 (7)	22 (7)	110	72.0	45.1–109
30–39	13219 (14)	36 (11)	89.2	28.8	20.2–39.9
40–49	21010 (22)	52 (16)	81.2	13.7	10.2–18.0
50–59	27487 (29)	91 (28)	117	10.9	8.8–13.4
60–69	17192 (18)	57 (18)	123	6.1	4.6–7.9
≥70	3008 (3)	13 (4)	180	5.3	2.8–9.1
Gender					
Male	59388 (61)	207 (64)	122	11.4	9.9–13.1
Female	37227 (39)	114 (36)	104	15.5	12.8–18.6
Race/ethnicity					
White, non-Hispanic	55662 (58)	240 (75)	146	14.2	12.5–16.1
Black	17074 (18)	29 (9)	63.2	9.2	6.2–13.2
Hispanic	17271 (18)	38 (12)	76.7	9.5	6.7–13.1
Asian/Pacific Islander	6608 (7)	14 (4)	71.1	9.4	5.1–15.8
Transplanted organ					
Kidney	57054 (59)	141 (44)	84.0	9.4	8.0–11.1
Pancreas or kidney-pancreas	4357 (5)	21 (7)	170	33.1	20.5–50.6
Liver	21143 (22)	73 (23)	124	12.7	10.0–16.0
Heart	7999 (8)	31 (10)	122	11.0	7.5–15.6
Lung	4170 (4)	44 (14)	415	41.3	30.0–55.5
Other or multiple	1892 (2)	11 (3)	265	32.2	16.1–57.6
Epstein-Barr viral serostatus					
Positive	46952 (49)	113 (35)	87.4	9.3	7.6–11.1

	Transplant Recipients n (%)[a]	DLBCL Cases n (%)[a]	IR[b]	SIR	95% CI
Negative	9215 (10)	81 (25)	309	43.6	34.6–54.2
Missing	40448 (42)	127 (40)	102	11.1	9.2–13.2
Transplant number					
First	86584 (90)	290 (90)	114	12.2	10.8–13.7
Second	9144 (10)	28 (9)	117	17.1	11.4–24.7
Third or higher	887 (1)	3 (1)	143	27.6	5.7–80.8
Calendar year of transplant					
2000–2004	57801 (60)	249 (78)	110	12.1	10.6–13.7
2005–2008	38814 (40)	72 (22)	135	14.7	11.5–18.5
Polyclonal antibodies					
No	73101 (76)	248 (77)	113	12.3	10.8–13.9
Yes	23514 (24)	73 (23)	120	13.6	10.7–17.1
IL2 receptor antagonists					
No	69618 (72)	243 (76)	123	13.4	11.7–15.2
Yes	26997 (28)	78 (24)	95.4	10.6	8.4–13.3
Site of DLBCL[c]					
Lymph nodes	94723	151 (49)	54.8	9.7	8.3–11.4
Transplant site	94723	32 (10)	11.6	186	127–263
Other extranodal	94723	127 (41)	46.1	13.3	11.1–15.9

IR: Incidence rate; SIR: Standardized incidence ratio; 95% CI: 95% Confidence interval; IL2: Interleukin-2

[a] Percentages may not add to 100 due to rounding

[b] Crude incidence rate per 100,000 person-years

[c] Site-specific analyses included only kidney, pancreas or kidney-pancreas, liver, heart, and lung transplants

Table 2

Associations between selected recipient and transplant characteristics and risk of early-onset (≤2 years after transplant) and late-onset (>2 years after transplant) diffuse large B-cell lymphoma in solid organ transplant recipients from 2000–2008 in the United States

	Early-onset DLBCL EBV-negative recipients				Early-onset DLBCL EBV-positive recipients				Late-onset DLBCL EBV-positive recipients			
	DLBCL Cases	SIR	RR[a]	95% CI	DLBCL Cases	SIR	RR[a]	95% CI	DLBCL Cases	SIR	RR[a, b]	95% CI
All transplants	70	78.7			72	11.8			41	6.7		
Age at transplant												
0–19	22	2123	39.0	20.3–77.0	13	675	69.4	33.8–137	1	43.4	X	x
20–39	16	294	5.6	2.7–11.4	11	33.1	2.6	1.2–5.5	4	11.2	1.9	0.4–6.1
40–49	7	59.2	1.3	0.5–3.0	12	14.3	1.2	0.6–2.4	8	8.8	1.6	0.6–3.8
50–59	15	52.8	1.0	reference	22	11.3	1.0	reference	13	6.3	1.0	reference
≥60	10	23.7	0.4	0.2–0.9	14	4.7	0.5	0.2–0.9	15	5.4	0.9	0.4–1.9
Transplanted organ												
Kidney	35	77.0	1.0	reference	23	6.8	1.0	reference	12	3.8	1.0	reference
Liver	8	34.4	0.6	0.2–1.2	16	11.6	2.0	1.0–3.7	18	12.5	3.5	1.7–7.4
Heart	9	89.4	1.5	0.7–2.9	6	8.4	1.4	0.5–3.2	4	4.4	1.3	0.4–3.7
Lung	16	249	3.8	2.1–6.8	11	26.7	4.6	2.1–9.2	6	16.6	4.7	1.6–12.1
Polyclonal antibodies												
No	45	61.9	1.0	reference	51	11.0	1.0	reference	37	7.6	1.0	reference
Yes	25	154	2.9	1.6–5.0	21	14.1	1.1	0.6–1.9	4	3.2	0.5	0.1–1.5
IL2 receptor antagonists												
No	50	79.8	1.0	reference	59	14.0	1.0	reference	27	6.4	1.0	reference
Yes	20	76.1	1.0	0.6–1.8	13	6.9	0.5	0.3–0.9	14	7.3	1.1	0.5–2.2

SIR: Standardized incidence ratio; RR: relative risk; EBV: Epstein-Barr viral serostatus; IL2: Interleukin-2

[a] Poisson regression models adjusted for age at transplant, gender, race/ethnicity, transplanted organ, and calendar year of transplant

[b] RRs not calculated for strata with less than 3 DLBCL cases (denoted by x)

Table 3

Associations between selected transplant characteristics and risk of diffuse large B-cell lymphoma in solid organ transplant recipients from 2000–2008 in the United States, stratified by DLBCL occurring in the transplanted organ, other extranodal sites, or in lymph nodes.

	DLBCL in the Transplanted Organ			DLBCL in Other Extranodal Sites			DLBCL in Lymph Nodes		
	Cases	**SIR**	**95% CI**	**Cases**	**SIR**	**95% CI**	**Cases**	**SIR**	**95% CI**
All transplants	32	186	(127–263)	127	13.3	(11.1–15.9)	151	9.7	(8.3–11.4)
EBV Serostatus									
Negative	7	543	(218–1119)	30	43.8	(29.6–62.6)	43	37.8	(27.4–50.9)
Positive	11	130	(65.0–233)	46	10.0	(7.4–13.4)	48	6.5	(4.8–8.6)
Transplanted Organ[a]									
Kidney	8	101	(43.8–200)	66	11.6	(9.0–14.8)	67	7.3	(5.7–9.3)
Liver	12	231	(119–404)	24	11.1	(7.1–16.5)	37	10.5	(7.4–14.5)
Heart	0	0	(0–176)	17	16.2	(9.5–26.0)	14	8.0	(4.4–13.4)
Lung	11	625	(312–1117)	11	28.8	(14.4–51.5)	22	33.1	(20.7–50.1)

SIR: Standardized incidence ratio; RR: Relative risk; 95% CI: 95% Confidence interval; EBV: Epstein-Barr virus

[a]Other transplanted organ types not shown